

What is claimed is:

1. An agent comprising:
a therapeutic component, and
a targeting component,
5 wherein the targeting component selectively binds at the
alpha-2B or alpha-2B/alpha-2C adrenergic receptor
subtype(s) as compared to the alpha-2A adrenergic
receptor subtype.
- 10 2. An agent according to claim 1 wherein the
therapeutic component interferes with the release of
neurotransmitters from a cell or its processes.
3. An agent according to claim 2 wherein the
15 therapeutic component comprises a light chain component.
4. An agent according to claim 2 wherein the light
chain component comprises a light chain or a fragment
thereof of a botulinum toxin, a butyricum toxin, a tetani
20 toxin or variants thereof.
5. An agent according to claim 2 wherein the light
chain component comprises a light chain or a fragment
thereof of a botulinum toxin type A, B, C₁, D, E, F, G or
25 variants thereof.
6. An agent according to claim 2 wherein the light
chain component comprises a light chain or a fragment
thereof of a botulinum toxin type A or variants thereof.
- 30 7. An agent according to claim 1 wherein the
therapeutic component inactivates cellular ribosomes.
8. An agent according to claim 7 wherein the
35 therapeutic component is saporin.

9. An agent according to claim 1 which further comprises a translocation component.

5 10. An agent according to claim 9 wherein the translocation component facilitates the transfer of at least a part of the agent into the cytoplasm of the target cell.

10 11. An agent according to claim 9 wherein the translocation component facilitates the transfer of the therapeutic component into the cytoplasm of the target cell.

15 12. An agent according to claim 9 wherein the translocation component comprises a heavy chain component.

20 13. An agent according to claim 12 wherein the heavy chain component comprises a heavy chain or a fragment thereof of a botulinum toxin, a butyricum toxin, a tetani toxin or variants thereof.

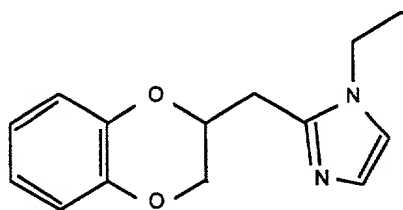
25 14. An agent according to claim 12 wherein the heavy chain component comprises a heavy chain or a fragment thereof of a botulinum toxin type A, B, C₁, D, E, F, G or variants thereof.

30 15. An agent according to claim 12 wherein the heavy chain component comprises a heavy chain or a fragment thereof of a botulinum toxin type A or variants thereof.

16. An agent according to claim 12 wherein the fragment of the heavy chain comprises at least a portion of the amino terminal fragment of the heavy chain.

17. An agent according to claim 1 wherein the therapeutic component comprises a light chain of a botulinum toxin type A and the translocation component comprises a fragment of a heavy chain of a botulinum toxin type A, wherein the fragment of a heavy chain can assist in the translocation of at least the therapeutic component into a cytoplasm of a cell.

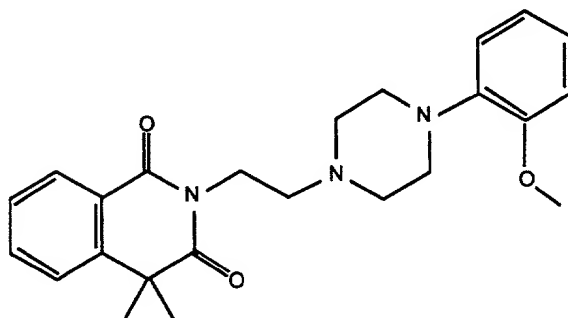
18. An agent according to claim 1 wherein the targeting component is represented by the formula:



Imiloxan

I.

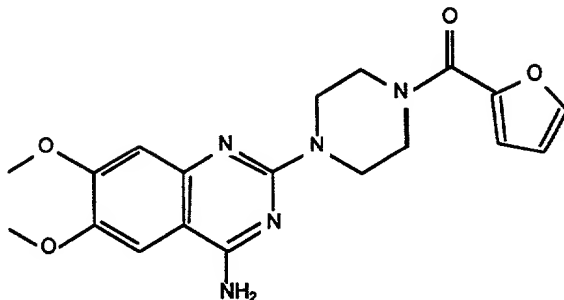
19. An agent according to claim 1 wherein the targeting component is a compound represented by the formula:



ARC 239

II.

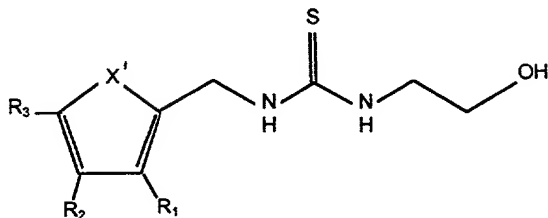
20. An agent according to claim 1 wherein the targeting component is a compound represented by the formula



Prazosin

III.

21. An agent according to claim 1 wherein the targeting component is a compound represented by the formula:



IV.

wherein X' is selected from the group consisting of $R_4-C=C-R_5$ and R_4-C ;

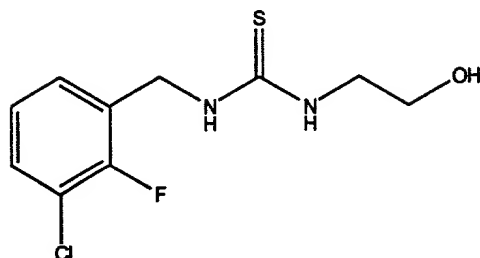
a six membered carbon ring structure is formed when

X' is $R_4-C=C-R_5$;

a five membered carbon ring is formed when X' is R_4-C ;

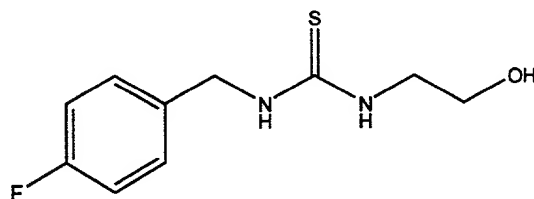
R_1 , R_2 , R_3 , R_4 and R_5 are each independently selected from the group consisting of F, Cl, Br, I, OR_6 and H, wherein R_6 is H or an alkyl, including a methyl, an ethyl or a propyl.

22. An agent according to claim 1 wherein the targeting component is a compound represented by the formula:



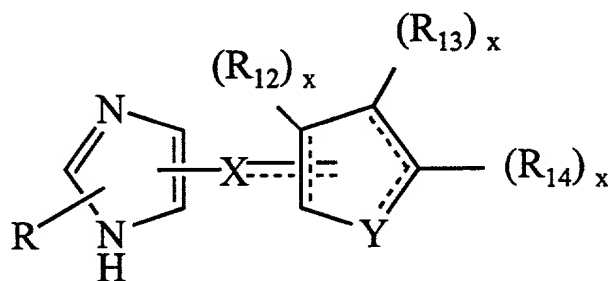
V.

23. An agent according to claim 1 wherein the targeting component is a compound represented by the formula:



VI.

24. An agent according to claim 1 wherein the targeting component is represented by the formula

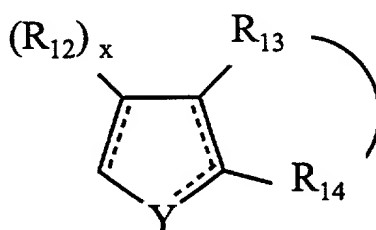


VII.

wherein the dotted lines represent optional double bonds;
R is H or lower alkyl; X is S or C(H)R₁₁, wherein R₁₁ is H
or lower alkyl or R₁₁ is absent when X is S or when the
bond between X and the ring represented by



5 is a double bond; Y is O, N, S, $(C(R_{11})X)_y$, wherein y is
 an integer of from 1 to 3,
 -CH=CH- or $-Y_1CH_2-$, wherein Y_1 is O, N or S; x is an
 integer of 1 or 2, wherein x is 1 when R_{12} , R_{13} or R_{14} is
 bound to an unsaturated carbon atom and x is 2 when R_{12} ,
 10 R_{13} or R_{14} is bonded to a saturated carbon atom; R_{12} is H,
 lower alkyl, halogen, hydroxy, lower alkoxy, lower
 alkenyl, acyl or lower alkynyl or, when attached to a
 saturated carbon atom, R_{12} may be oxo; R_{13} and R_{14} are,
 each, H, lower alkyl, halogen, lower alkenyl, acyl or
 15 lower alkynyl, or, when attached to a saturated carbon
 atom, R_{12} may be oxo; R_{13} and R_{14} are, each, H, lower
 alkyl, halogen, lower alkenyl, acyl, lower alkynyl, aryl,
 heteroaryl, or substituted aryl or heteroaryl, wherein
 said substituent is halogen, lower alkyl, lower alkoxy,
 20 lower alkenyl, acyl, lower alkynyl, nitro, cyano,
 trifluoromethyl, hydroxy, or phenyl or, together, are -
 $(C(R_2)x)z-$; $-Y_1(C(R_2)x)z'-$; $-Y_1(C(R_2)x)Y_1-$; $-(C(R_2)x)-$
 $Y_1-(C(R_2)x)-$; $-(C(R_2)x)-Y_1-(C(R_2)x)-(C(R_2)x)-$ and $-Y_1-$
 $(C(R_2)x)-Y_1-(C(R_2)x)-$ wherein z is an integer of from 3
 25 to 5, z' is an integer of from 2 to 4 and x and y are as
 defined above, and further either end of each of these
 divalent moieties may attach at either R_{13} or R_{14} to form
 the condensed ring structure



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and the ring thus formed may be totally unsaturated,
 partially unsaturated, or totally saturated provided that

a ring carbon has no more than 4 valences, nitrogen no more than three and O and S have no more than two.

25. An agent according to claim 1 wherein the targeting
5 component comprises an amino acid component.

26. An agent according to claim 25 wherein the amino acid component is an antibody.

10 27. An agent according to claim 26 wherein the antibody is raised from an antigen component, the antigen component comprises a second extracellular loop of an alpha-2B receptor.

15 28. An agent according to claim 27 wherein the second extracellular loop is conjugated to a keyhole limpet hemocyanin.

20 29. An agent according to claim 27 wherein the second extracellular loop comprises a peptide fragment comprising an amino acid sequence of KGDQGPQPRGRPQCKLNQE (SEQ ID#1).

25 30. An agent according to claim 25 wherein the amino acid component comprises a variant peptide, a variant polypeptide, a variant protein or a variant protein complex of a wild type peptide, polypeptide, protein or protein complex, respectively.

30 31. An agent according to claim 25 wherein the amino acid component is a variant polypeptide.

32. An agent according to claim 31 wherein the variant polypeptide is a variant heavy chain.

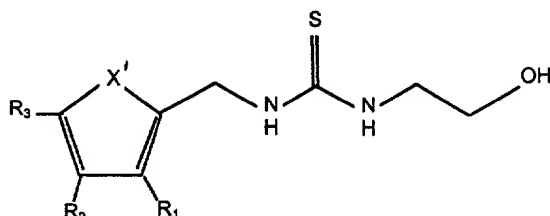
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33. An agent according to claim 1 wherein the

therapeutic component and the targeting component are attached to each other through a spacer component.

34. An agent according to claim 9 wherein the therapeutic component, the translocation component and the targeting component are attached to each other through a spacer component.

35. An agent according to claim 34 wherein the therapeutic component is a light chain of a botulinum toxin type A, the translocation component is a fragment of a heavy chain of a botulinum toxin type A which can facilitate the translocation of at least the light chain into a cytoplasm of a cell, and the targeting component is represented by the formula:



IV.

wherein X' is selected from the group consisting of $R_4-C=C-R_5$ and R_4-C ;

a six membered carbon ring structure is formed when X' is $R_4-C=C-R_5$;

a five membered carbon ring is formed when X' is R_4-C ;

R_1 , R_2 , R_3 , R_4 and R_5 are each independently selected from the group consisting of F, Cl, Br, I, OR_6 and H, wherein R_6 is H or an alkyl, including a methyl, an ethyl or a propyl.

36. An agent according to claim 34 wherein the spacer component comprises a moiety selected from the group consisting of a hydrocarbon, a polypeptide other than an immunoglobulin hinge region, and a proline-containing polypeptide identical or analogous to an immunoglobulin hinge region.

37. An agent according to claim 1 useful for treating chronic pain in a mammal, including a human.

38. An agent according to claim 37 wherein the chronic pain is treated without substantially affecting acute pain sensation or tactile sensation.

39. A method for making an agent for treating pain comprising the step of producing a polypeptide from a gene having codes for at least one component of the agent, wherein the agent comprises

a therapeutic component, and

a targeting component,

wherein the targeting component selectively binds at the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtype(s) as compared to the alpha-2A adrenergic receptor subtype.

40. A method for making an agent according to claim 39 wherein the agent further comprises a translocation component.

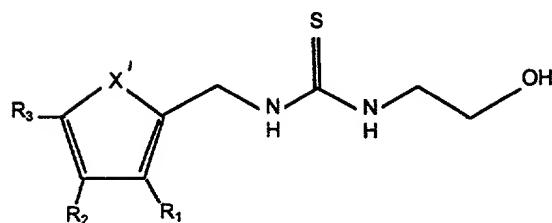
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41. A method according to claim 40 wherein the therapeutic component comprises a light chain of botulium toxin type A and the translocation component comprises a fragment of a heavy chain which is able to facilitate the transfer of at least the light chain into the cytoplasm of the target cell.

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42. A method according to claim 40 wherein the targeting component comprises an amino acid component.
- 5 43. A method according to claim 42 wherein the amino acid component comprises a variant peptide, a variant polypeptide, a variant protein, or a variant protein complex of a wild type peptide, polypeptide, protein or protein complex.
- 10 44. A method according to claim 43 wherein the variant peptide is a variant heavy chain.
- 15 45. A method for treating pain comprising the step of administering to a mammal a therapeutically effective amount of an agent to alleviate pain, the agent comprises a therapeutic component, and a targeting component, wherein the targeting component selectively binds at the
- 20 alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtype(s) as compared to the alpha-2A adrenergic receptor subtype.
- 25 46. A method according to claim 45 wherein the pain alleviated is chronic pain.
47. A method for treating pain according to claim 45 which further comprises a translocation component.
- 30 48. A method according to claim 47 wherein the therapeutic component comprises a light chain of botulium toxin type A; the translocation component comprises a fragment of the heavy chain of botulinum toxin type A which is able
- 35 to facilitate the transfer of at least the light chain into the cytoplasm of the target cell; and

targeting component is represented by the general formula:



IV.

wherein X' is selected from the group consisting of $R_4-C=C-R_5$ and R_4-C ;

a six membered carbon ring structure is formed when X' is $R_4-C=C-R_5$;

a five membered carbon ring is formed when X' is R_4-C ;

R_1 , R_2 , R_3 , R_4 and R_5 are each independently selected from the group consisting of F, Cl, Br, I, OR_6 and H, wherein R_6 is H or an alkyl, including a methyl, an ethyl or a propyl.

49. A method according to claim 47 wherein the therapeutic component and the translocation component are part of a botulinum toxin.

50. A method according to claim 49 wherein the botulinum toxin is type A.

51. A method according to claim 50 wherein the agent comprises about 1 U to about 500 U of the botulinum toxin.

52. A method according to claim 50 wherein the agent comprises about 10 U to about 300 U of the botulinum toxin.

53. A method according to claim 50 wherein the pain alleviation persists from about 2 to about 27 months.

5 54. A method according to claim 45 wherein the agent is administered intrathecally.

55. A method according to claim 45 wherein the agent is administered intrathecally to a cranial region of the
10 central nervous system.

56. A method according to claim 45 wherein the agent is administered intrathecally to a cervical region of the
15 central nervous system.

57. A method according to claim 45 wherein the agent is administered intrathecally to a thoracic region of the
20 central nervous system.

58. A method according to claim 45 wherein the agent is administered intrathecally to a lumbar region of the
25 central nervous system.

59. A method according to claim 45 wherein the agent is administered intrathecally to a sacral region of the
30 central nervous system.

60. A method according to claim 45 wherein the agent is administered intramuscularly.

61. A method according to claim 45 wherein the agent is administered subcutaneously.

62. A method according to claim 45 wherein the pain is
35 chronic pain.

63. A method according to claim 45 wherein the pain is visceral pain.

5 64. A method according to claim 45 wherein the pain is neuropathic pain.

65. A method according to claim 45 wherein the pain is referred pain.

10 66. A method according to claim 45 wherein the pain is a allodynia type pain.

15 67. A method according to claim 63 wherein the allodynia type pain is alleviated without substantially affecting acute pain sensation or tactile sensation.